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Respiratory system impedance with impulse oscillometry in healthy and COPD subjects: ECLIPSE baseline results

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Respiratory reactance

Summary
Rationale: Current assessment of COPD relies extensively on the use of spirometry, an effort-dependent maneuver. Impulse oscillometry (IOS) is a non-volitional way to measure respiratory system mechanics, but its relationship to structural and functional measurements in large groups of patients with COPD is not clear.
Objectives: We evaluated the ability of IOS to detect and stage COPD severity in the prospective ECLIPSE cohort of COPD patients defined spirometrically, and contrasted with smoking and non-smoking healthy subjects. Additionally, we assessed whether IOS relates to extent of CT-defined emphysema.
Methods: We measured lung impedance with IOS in healthy non-smokers ($n = 233$), healthy former smokers ($n = 322$) or patients with COPD ($n = 2054$) and related these parameters with spirometry and areas of low attenuation in lung CT.

Abbreviations: COPD, chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IOS, impulse oscillometry; CT, computed tomography; FEV_1, forced expired volume in 1 s; SVC, slow vital capacity; FVC, forced vital capacity; FRC, functional residual capacity; R_5, R_{15} and R_{20}, respiratory resistance (R_{rs}) at 5 Hz, 15 Hz, and 20 Hz, respectively; $R_5 - R_{20}$, difference in respiratory resistance at 5 Hz and 20 Hz; AX, integrated area of low-frequency reactance; CV, coefficient of variation; X_5, reactance at 5 Hz; F_{Res}, resonant frequency; LAA%, percentage of low attenuation areas (i.e. below −950 Hounsfields Units) on chest computed tomography; BMI, body mass index.

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Measurements and main results: In healthy control subjects, IOS demonstrated good repeatability over 3 months. In the COPD group, respiratory system impedance was worse compared with controls as was frequency dependence of resistance, which related to GOLD stage. However, 29–86% of the COPD subjects had values that fell within the 90% confidence interval of several parameters of the healthy non-smokers. Although mean values for impedance parameters and CT indices worsened as GOLD severity increased, actual correlations between them were poor ($r \leq 0.16$).
Conclusions: IOS can be reliably used in large cohorts of subjects to assess respiratory system impedance. Cross-sectional data suggest that it may have limited usefulness in evaluating the degree of pathologic disease, whereas its role in assessing disease progression in COPD currently remains undefined.

Background

Although chronic obstructive pulmonary disease (COPD) is increasingly recognized for its associated systemic manifestations,[1,2] the diagnosis and severity of airflow limitation requires the spirometric measurement of pulmonary function, as indicated by the forced expired volume in 1 s (FEV_1).[3] Moreover, the current international COPD treatment guidelines proffer both pharmacologic and non-pharmacologic recommendations based principally on the FEV_1. While spirometry is considered the standard by which airflow limitation is assessed, it is well known that patient effort and cooperation is required for optimal validity and reproducibility.[4] Somewhat more complex tests to assess pulmonary function include measurement of lung volumes, airways resistance (R_{aw}) or its reciprocal conductance (G_{aw}) with body plethysmography, or assessment of gas exchange by diffusion of carbon monoxide (e.g. D_LCO). However, assessments using plethysmography or determination of single-breath carbon monoxide diffusion also require patient cooperation. Therefore, there is great interest in developing techniques that measure lung physiology independent of patient effort.

Determination of the impedance on the respiratory system using imposed forced oscillations at the mouth has been described since the 1950s.[5] Current technology allows impedance and its components, resistance and reactance, to be measured during tidal breathing with little to no cooperation on the part of the patient.[6] Previous investigators have characterized impedance parameters in children and adults, with conditions such as asthma and COPD, as well as in World Trade Center emergency workers exposed to inhaled dust following the September 2001 terrorist attack.[7–9] However, while forced oscillation has its advantages, most studies have been conducted by single investigators or centers and for a technique to be useful, it is necessary that it be reproducible and valid across centers.

The Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) trial was initiated to identify potential parameters that may predict disease progression in individuals with different COPD subtypes and to identify biomarkers and/or other non-spirometric parameters that may serve as surrogate endpoints.[10] The ECLIPSE cohort is being evaluated using quantitative computed tomography (CT) of the lungs, providing unique information about the degree of emphysema and airway compromise. In this descriptive analysis of the baseline data, we sought to assess lung impedance parameters in this large cohort of subjects with COPD and to compare them with both healthy non-smoking and smoking control subjects, across several centers on two continents. We also hypothesized that respiratory system impedance parameters could relate to the anatomical lung parenchymal correlates, as assessed by CT. Our intention was not to use impedance measurements as a replacement for conventional spirometry in the diagnosis of COPD but to determine whether differences exist within spirometrically defined groups of COPD patients that could be reliably measured and which might identify phenotypically different behaviors during the subsequent follow up period.

Methods

The design of the ECLIPSE trial has been previously described in detail.[10] In brief, ECLIPSE is a 3-year longitudinal prospective study designed to identify novel endpoints and compare these with FEV_1 for their ability to measure and predict COPD severity and its progression over time. We recruited 2164 COPD subjects aged 40–75 years inclusive with a $\geq$10 pack-year smoking history, a post-bronchodilator $FEV_1 < 80\%$ predicted and the FEV_1 to forced vital capacity (FVC) ratio $\leq$0.70. This analysis is restricted to the 2054 subjects with COPD who also had valid baseline impulse oscillometry (IOS) measurements and the control subjects who were either current/former smokers ($\geq$10 pack-year smoking history; $n = 322$) or non-smokers ($<$1 pack-year; $n = 233$), aged 40–75 years with a post-bronchodilator $FEV_1 > 85\%$ and a $FEV_1/FVC > 0.70$.

Pulmonary function and IOS measurements

Spirometry and IOS were performed in the following order: IOS, slow vital capacity (SVC), then spirometry. Pre- and post-bronchodilator (400 μg of albuterol) IOS, SVC, FEV_1, FVC, FEV_1/FVC, and FEV_6 were performed at each visit with the Jaeger MasterScope CT Impulse Oscillometry System (Hoechberg, Germany). Spirometry was performed according to American Thoracic Society (ATS) guidelines.[3] Post-bronchodilator FEV_1 percentage predicted was determined using the European Community Coal and Steel standards.[11]

IOS was performed seated using a noseclip and a mouthpiece that stabilized the tongue position and the cheeks supported. Impulses were delivered for 20 s during tidal breathing. A minimum of three maneuvers were performed and all acceptable data tracings were transferred by the investigator to a central database at Viasys Healthcare Clinical Services (Hoechberg, Germany). The data were initially analyzed by computer algorithms based on the European Respiratory Society (ERS) Task Force on forced oscillation technique testing.[6] The tracings were then overread by trained specialists at Viasys Healthcare Clinical Services for overall quality, and for reproducibility of the respiratory resistance (R_{rs}) at 5 Hz, 20 Hz, and the integrated area of low-frequency reactance (coefficient of variation [CV] of selected tracings $\leq$10%, $\leq$15% and $\leq$15%, respectively), as well as compliance with ERS criteria. Specified IOS parameters for analysis included: R_{rs} at 5, 15 and 20 Hz (R_5, R_{15} and R_{20}); reactance at 5 Hz (X_5) and the integrated area of low-frequency reactance (AX) from 5 Hz to resonant frequency (F_{Res}). In addition, R_5-R_{20} was determined as an index of frequency dependence of resistance.

Whole-body plethysmography was performed at selected investigator sites, but with no attempt made to standardize plethysmographic equipment across the sites. However, each site submitted a complete plethysmography report to a central reader; the report included the graphics for functional residual capacity (FRC), R_{aw} and SVC, as well as numerical data from all trials, including panting frequency. The central reader assessed each individual trial for acceptability and each test session for repeatability based on published recommendations.[12,13] Reference values for residual volume, FRC and total lung capacity (TLC) were from the ATS/ERS workshop report.[14]

Quantitative chest CT

Baseline CT scans were performed within one day of spirometry. All scans were acquired using multi detector-row CT scanners (GE Healthcare or Siemens Healthcare) with a minimum of four rows and obtained in the supine position, at suspended full inspiration without administration of intravenous contrast. Exposure settings were 120 kVp and 40 mA, and images were reconstructed using 1.0 mm (Siemens Healthcare) or 1.25 mm (GE Healthcare) contiguous slices and a low spatial frequency reconstruction algorithm (GE Healthcare: standard, Siemens Healthcare: b35f). CT scanners were calibrated regularly using industry and institutional standards.

All CT scans were analyzed using 'Pulmonary Workstation 2.0' software (VIDA Diagnostics, Iowa City, IA, USA) following segmentation of the individual lobes.[15] The extent of emphysema (percentage of low attenuation areas [LAA%]) was estimated using the threshold technique quantifying the percent of the total lung voxels with an apparent X-ray attenuation value below $-$950 Hounsfields Units (HU).[16] CT scans were assessed to confirm that they met the study protocol and those that did not were excluded from analysis. CT scans that contained a significant proportion of artifact, such as motion and excessive noise, which caused the lung analysis software to fail during the procedure were also excluded from study ($N = 348$, 13%).

Statistical analysis

Results are shown as mean $\pm$ standard deviation (SD), median values (interquartile range), frequency distribution or percentage, as appropriate. Analyses of variance and Cochran-Mantel-Haenszel tests, as appropriate, were used to assess differences among the cohorts. IOS parameter differences were determined after adjustment for age and gender. Reproducibility of lung function measurements was assessed through Bland–Altman plots.[17] Pearson correlation coefficients were calculated to evaluate the relationships between lung function and other clinical assessments. In order to calculate normal predictive equations, linear and multiple regression were conducted. Predictors in the regression models were age, gender, height, weight, and body mass index (BMI).[18] *P* values less than 0.05 were considered significant. SAS® Version 9.1 was used to carry out all analyses. Only those subjects with at least one IOS measurement were included in these analyses.

Results

Baseline characteristics

Table 1 summarizes the baseline demographics of the ECLIPSE populations. Subjects with COPD were older than both the smoking and non-smoking controls and constituted a higher percentage of males. A greater percentage of the smoking controls were current smokers compared with the COPD subjects. In addition, 72% of the subjects with COPD were receiving therapy with an ICS either alone or in combination with a long-acting bronchodilator.

The COPD subjects had a level of airflow obstruction that on average was moderate-to-severe; 45% were Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage 2, 42% were GOLD stage 3, and 14% were GOLD stage 4. COPD subjects with GOLD stage 4 severity were of a similar age and had similar tobacco exposure compared with subjects of less severe disease; however, fewer of these more severe subjects were current smokers.

The variability of the spirometry results between the baseline and 3-month visit timepoints was similar for the COPD subjects and the controls (Fig. 1). This similarity existed despite the fact that 577/2054 (28%) subjects with COPD had an exacerbation in the 3 month period between baseline and Visit 2. Of these, 257 resolved within the month prior to Visit 2. The remainder resolved more than 1 month prior to Visit 2. Three hundred forty-eight (17%) of the COPD subjects had a change in their medications during this 3 month period. In all 763 (37%) had either an exacerbation or changed medications during the period from baseline to the 3 month visit. For most subjects with COPD, spirometry was fairly reproducible between these two visits. The coefficient of repeatability (i.e. the value that 95% of differences between two measurements on the same subject would not exceed) was 0.40 L in the subjects with COPD and it was 0.46 L for the combined group of non-smoking and smoking control subjects.

Technically acceptable post-bronchodilator body plethysmographic maneuvers were obtained in a subset of control and COPD subjects (17 non-smoking controls, 166 smoking

Table 1 Baseline demographics of ECLIPSE subjects.

	NSC (n = 233)	CS (n = 322)	COPD (n = 2054)	GOLD 2 (n = 915)	GOLD 3 (n = 861)	GOLD 4 (n = 278)
Age, years	54.3 (9.0)	55.2 (9.0)	63.4(7.1)[a]	63.5 (7.2)	63.7 (7.0)	62.4 (7.0)[b,c]
Male gender No. (%)	85 (36)	178 (55)[d]	1341 (65)[a]	550 (60)	584 (68)[b]	207 (74)[b,c]
BMI (kg/m^2)	27.6 (5.4)	26.8 (4.5)	26.5 (5.6)[d]	27.3 (5.7)	26.1 (5.4)[b]	25.0 (5.7)[b,c]
Current smokers No. (%)	0[e]	194 (60)[d]	746 (36)[a]	350 (38)	321 (37)	75 (27)[f]
Pack-years	0.0 (0.1)	31.5 (21.5)[d]	48.7 (27.2)[a]	48.2 (28.4)	48.9 (25.7)	50.0 (27.6)
Lung function: FEV_1 (L)	3.26 (0.78)	3.35 (0.76)	1.35 (0.52)[a]	1.75 (0.45)	1.13 (0.27)[b]	0.72 (0.16)[f]
FEV_1 (% predicted)	114.8 (13.8)	108.9 (12.0)[d]	48.4 (15.7)[a]	63.1 (8.4)	40.3 (5.8)[b]	24.8 (3.7)[f]
FEV_1/FVC (×100)	81.0 (5.2)	79.3 (5.1)	44.6 (11.6)[a]	52.7 (8.8)	40.2 (8.8)[b]	31.7 (7.3)[f]
% reversibility	2.8 (4.5)	4.5 (5.6)	10.7 (13.6)[a]	11.1 (12.5)	11.1 (14.5)	8.2 (14.0)[f]
LAA% on CT	4.1 (4.2)	2.4 (3.1)	17.7 (12.2)[a]	12.2 (9.6)	20.1 (11.6)[b]	28.6 (12.4)[f]

Data expressed as mean (SD) unless otherwise specified; Lung function parameters are post-bronchodilator. NSC = non-smoker controls; CS = control smokers; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; FEV_1 = forced expired volume in 1 s; FVC = forced vital capacity; BMI = body mass index; LAA% = percentage of low attenuation areas (i.e. below −950 Hounsfields Units) on chest computed tomography; CT = computed tomography.

[a] $p < 0.001$ compared with NSC and CS.

[b] $p < 0.001$ compared with GOLD 2 ($p = 0.029$ for age).

[c] $p < 0.04$ compared with GOLD 3.

[d] $p < 0.001$ compared with NSC ($p = 0.003$ for BMI).

[e] 11 (5%) of NSC were former smokers.

[f] $p \leq 0.002$ compared with GOLD 2 and GOLD 3 ($p = 0.003$ for percentage reversibility).

controls and 582 COPD subjects). Spirometric indices in this subset of subjects were similar to their respective cohort in the entire population. Subjects with COPD demonstrated evidence of air trapping (FRC 145.0 ± 34.3% predicted) and reduced specific conductance (SGaw) compared with both control groups (online Table 1).

IOS parameters

Non-smoking and smoking control subjects

Values (mean ± SD) at baseline for R_5, R_{20}, $R_5 - R_{20}$, X_5, AX and F_{Res} from the 233 non-smoking control subjects with a <1 pack-year smoking history and smoking control subjects are shown in Table 2. Bland–Altman plots were constructed from the baseline and 3-month data for the respiratory system resistance at 5 Hz, R_5 (Fig. 2) and also for R_{20}, $R_5 - R_{20}$, AX and X_5 (online Fig. 1). Impedance parameters in this group were fairly stable over this 3-month period. The coefficient of repeatability for R_5 for the non-smoking and smoking controls combined was 0.13 kPa/L/s.

Of the smoking control subjects 95%, 93%, 94% and 95% had values that fell within the normal range (i.e. 90% confidence interval of the non-smoking controls) for R_5, R_{20}, $R_5 - R_{20}$, and AX, respectively. The smoking control subjects with elevated values had a similar degree of CT-assessed emphysema as the non-smoking controls. Thus, the mean ± SD LAA% in the 14/322 smoking control subjects with an elevated R_5 was 2.5 ± 3.4% compared with

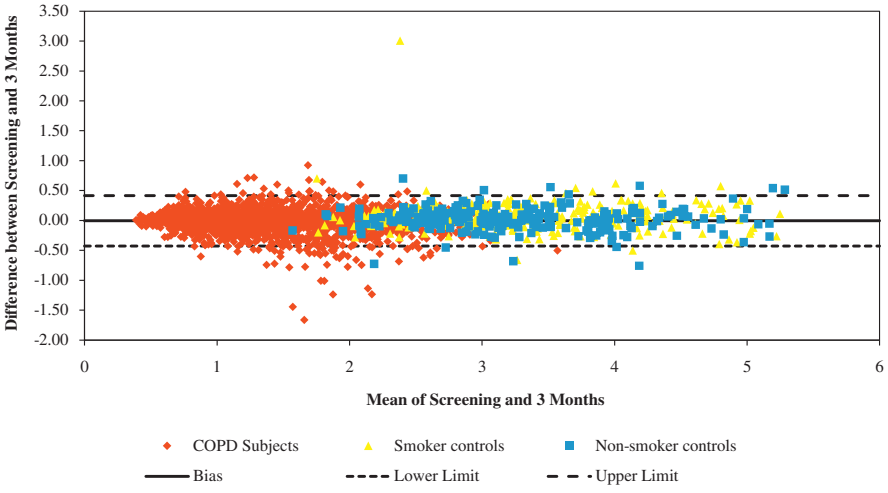

Figure 1 Bland–Altman plots depicting the reproducibility between the baseline values and measurements at 3 months for FEV_1 (forced expiratory volume in 1 s) from non-smoking and smoking control, and COPD (chronic obstructive pulmonary disease) subjects. The central horizontal line shows mean of differences and the dashed lines represent the 95% limits of agreement.

Table 2 Baseline IOS (impulse oscillometry) impedance parameters in ECLIPSE subjects.

	NSC[a] (n = 233)	CS (n = 322)	COPD (n = 2054)	GOLD 2 (n = 915)	GOLD 3 (n = 861)	GOLD 4 (n = 278)
R_5 (kPa/L/s)	0.33 (0.10)	0.31 (0.10)	0.49 (0.16)[b]	0.45 (0.14)	0.51 (0.16)[c]	0.55 (0.19)[d]
R_{20} (kPa/L/s)	0.26 (0.07)	0.25 (0.07)[e]	0.30 (0.08)[b]	0.29 (0.07)	0.31 (0.08)[c]	0.31 (0.09)[f]
$R_5 - R_{20}$ (kPa/L/s)	0.07 (0.05)	0.06 (0.05)	0.19 (0.10)[b]	0.15 (0.09)	0.20 (0.10)[c]	0.24 (0.12)[d]
X_5 (kPa/L/s)	−0.10 (0.06)	−0.09 (0.05)	−0.29 (0.17)[b]	−0.21 (0.13)	−0.32 (0.16)[c]	−0.44 (0.18)[d]
AX (Hz·kPa/L/s)	0.38 (0.40)	0.34 (0.35)	1.99 (1.46)[b]	1.37 (1.08)	2.25 (1.36)[c]	3.23 (1.79)[d]
F_{Res} (Hz)	12.4 (3.4)	12.1 (3.2)	20.7 (5.2)[b]	18.3 (4.3)	21.8 (4.7)[c]	25.3 (5.5)[d]

Data expressed as mean (SD) unless otherwise specified; Impedance parameters are post-bronchodilator. NSC = non-smoker controls; CS = control smokers; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; $R_{5;}$ = respiratory resistance (R_{rs}) at 5 Hz; $R_{20;}$ = respiratory resistance (R_{rs}) at 20 Hz; $R_5 - R_{20}$ = difference in respiratory resistance at 5 Hz and 20 Hz; X_5 = reactance at 5 Hz; AX = integrated area of low-frequency reactance; F_{Res} = resonant frequency.

[a] 11 (5%) of NSC were former smokers.

[b] $p < 0.001$ compared with NSC and CS.

[c] $p \leq 0.001$ compared with GOLD 2.

[d] $p \leq 0.001$ compared with GOLD 2 and GOLD 3.

[e] $p = 0.041$ compared with NSC.

[f] $p = 0.002$ compared with GOLD 2. Comparisons between groups were adjusted for age and gender.

4.1 ± 4.2% in the non-smoking control subjects. Conversely, compared with the smoking control subjects who had normal AX, those with an elevated AX (15 of 322) had a significantly lower FEV_1 (102.9 ± 10.2% vs. 109.2 ± 12.0%, $p = 0.045$), a difference that was not observed in the non-smoking control subjects (114.9 ± 13.5% vs. 112.8 ± 18.2%, p = not significant). These smoking control subjects with an elevated AX were somewhat older (60.7 ± 8.9 years vs. 54.9 ± 8.9 years, $p = 0.014$), and a trend for a greater smoking history (39.6 ± 19.2 pack-years vs. 31.1 ± 21.6 pack-years, p = not significant), and 10 of these 15 subjects were current smokers compared with 184 (60%) of those with a normal AX.

Subjects with COPD

As have been previously observed,[8] the respiratory system impedance components of resistance and reactance were elevated in subjects with COPD; including low-frequency reactance area (Table 2), with evidence of frequency dependence of resistance, $R_5 - R_{20}$ (Table 2 and Fig. 3). Bland–Altman plots were constructed from the baseline and 3-month data for R_5 (Fig. 2) and also for R_{20}, $R_5 - R_{20}$, AX and X_5 (online Fig. 1). As with spirometry, following inhaled bronchodilators R_5, R_{20}, $R_5 - R_{20,}$ X_5 and AX decreased in subjects with COPD (of which the magnitude appeared to be related to GOLD status), and other than AX, also improved in controls (online Fig. 2). Interestingly, 61%, 86%, 40%, 34% and 29% of the COPD subjects with measurable baseline parameters of R_5, R_{20}, $R_5 - R_{20}$, X_5 and AX values respectively, had values that fell within the normal range.

The subjects with COPD had a greater degree of CT diagnosed emphysema (i.e. LAA%) than healthy non-smokers (17.7 ± 12.2% vs. 4.1 ± 4.2%, $p < 0.001$). The parameters of respiratory system impedance and CT index of LAA% worsened as GOLD stages increased (Tables 1 and 2). Despite this apparent relationship, the actual correlations between either LAA% with R_5, $R_5 - R_{20}$, or AX were

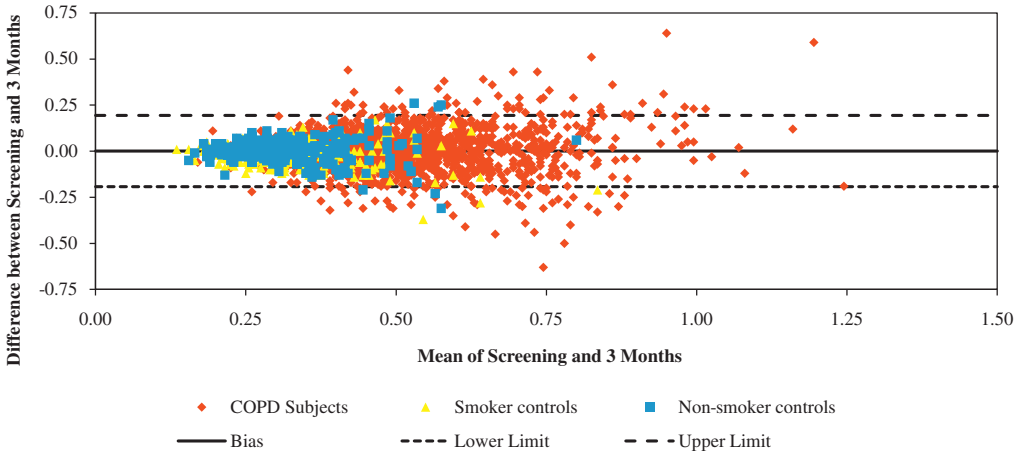

Figure 2 Bland–Altman plots depicting the reproducibility between the baseline values and measurements at 3 months for respiratory system resistance at R_5 (respiratory resistance (R_{rs}) at 5 Hz) from non-smoking and smoking control subjects and COPD (chronic obstructive pulmonary disease) subjects. The central horizontal line shows mean of differences and the dashed lines represent the 95% limits of agreement.

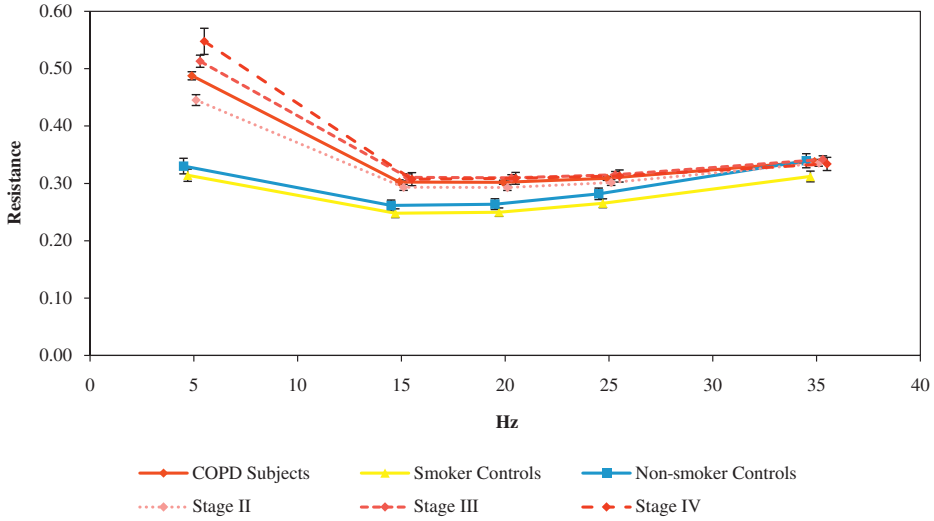

Figure 3 Frequency dependence of respiratory system resistance. Respiratory system resistance as a function of frequency for control and all COPD (chronic obstructive pulmonary disease) subjects, and by GOLD (Global Initiative for Chronic Obstructive Lung Disease) severity stage. Error bars are ±2 standard error of the mean.

poor (Pearson's $r \leq 0.16$). However, within a GOLD stage and compared with COPD subjects who had normal AX or R_5, COPD subjects with an abnormal AX tended to have a lower FEV_1, while subjects with an abnormal R_5 surprisingly tended to demonstrate less emphysema (i.e. lower LAA%, Table 3). Finally, for the COPD subjects, there were no significant correlations between any of the IOS parameters and pack years of smoking.

Other assessments

The spirometric parameter (the forced expiratory flow between 25% and 75% of the vital capacity FEF_{25-75}) has previously been viewed as a crude surrogate to assess the small airways. We therefore examined the correlation between this parameter and $R_5 - R_{20}$. The Pearson's correlation coefficient (r) for this relationship was −0.31 ($p < 0.001$) for the smoking control subjects and −0.34 ($p < 0.001$) for the COPD population (data not shown). Due to skewed distributions of R_{aw} and SG_{aw}, we have calculated Spearman correlation coefficients. The correlations between Raw and AX and X_5 are 0.65 and −0.68, respectively ($p < 0.001$). The correlations between SGaw and AX and X_5 are −0.56 and 0.57, respectively ($p < 0.001$).

Normative regression equations

We attempted to derive predictive regression equations for the IOS parameters based on the data collected in the non-smoking controls by linear and multiple regression. Each model for an IOS parameter included age, height, weight, gender, BMI and fat-free mass via bioimpedance. However, for both the linear and multiple regression for all IOS parameters, R^2 values were <0.40.

Pasker and colleagues derived predictive reference equations of a fourth degree polynomial for impedance parameters between 6 and 24 Hz in 226 healthy subjects using forced oscillation technique (FOT) generated with pseudo-random noise.[19] We therefore used Bland–Altman analysis to assess the degree of agreement between the measured values of R_{20} in our non-smoking controls with those predicted from Pasker's equation. Although approximately 95% of values fell within the limits of agreement, it appeared that at higher values of R_{20}, the predicted values tended to underestimate values directly obtained from IOS measurements (data not shown).

Discussion

This study of the baseline and 3-month data on the value of impulse oscillometry applied to the ECLIPSE cohort of COPD subjects provided several important findings. First, that IOS can be reliably obtained across centers in different continents. Second, several parameters of IOS differ between subjects with COPD and smoking and non-smoking controls, and help discriminate subjects with different degrees of airflow limitation as classified by the ATS/ERS/GOLD stages. Third, although some association exists between IOS measurements and degree of CT measured emphysema, they were modest and of limited clinical value.

Although COPD is a heterogeneous disease complex, only the presence of airflow limitation as determined by spirometry is required for the diagnosis in patients with an appropriate medical history. Conversely, the varied manifestations of the disease are not, in and of themselves, solely determined by the severity of the airflow limitation. The ECLIPSE trial was designed to identify potential novel endpoints that may subsequently provide a better characterization of different subtypes/phenotypes of COPD patients than currently accomplished with traditional spirometry. Our data do not suggest that IOS or any assessment of respiratory system impedance can be used as a replacement for spirometry in the diagnosis of COPD.

Compared with the relative stability of FEV_1 over short periods (i.e. 3 months), respiratory impedance appears slightly more variable over a similar time frame. This variability is not unique to our study and other investigators

Table 3 AX (integrated area of low-frequency reactance) and R_5 (respiratory resistance (R_{rs}) at 5 Hz) characteristics by GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage.

	GOLD stage 2				GOLD stage 3				GOLD stage 4			
Characteristic	Normal AX	Abnormal AX	Normal R_5	Abnormal R_5	Normal AX	Abnormal AX	Normal R_5	Abnormal R_5	Normal AX	Abnormal AX	Normal R_5	Abnormal R_5
N	442	473	650	264	133	726	466	394	14	263	135	142
FEV_1 (% predicted)	64.7 (8.2)[a]	61.6 (8.3)	63.8 (8.3)[a]	61.6 (8.4)	42.8 (4.8)[a]	39.9 (5.9)	40.6 (5.8)	40.1 (5.8)	23.9 (4.0)	24.9 (3.7)	25.0 (3.8)	24.7 (3.5)
LAA % on CT[b]	12.7 (10.2)	11.6 (8.9)	12.7 (9.8)[c]	10.7 (8.9)	20.7 (12.8)	19.9 (11.2)	21.8 (11.5)[a]	17.9 (11.0)	22.1 (13.8)	28.9 (12.3)	31.2 (11.8)[d]	26.3 (12.5)

Data expressed as mean (SD) unless otherwise specified. FEV_1 = forced expired volume in 1 s; LAA % = percentage of low attenuation areas (i.e. below −950 Hounsfields Units) on chest computed tomography; CT = computed tomography.

[a] $p < 0.001$ compared with subjects with abnormal impedance parameter.

[b] < −950 HU.

[c] $p = 0.012$ compared with subjects with abnormal impedance parameter.

[d] $p = 0.002$ compared with subjects with abnormal impedance parameter. Comparisons between groups were adjusted for age and gender.

have reported intra-individual variability either within-day[20,21] or day-to-day.[20–22] Van den Elshout[20] reported a within-day and day-to-day coefficient of variation (CV) of respiratory system resistance at 8 Hz (R_8) of 8.3% and 10.1%, respectively (in comparison, the respective CV for FEV_1 was 6.0% and 6.4%). Gimeno et al[21] reported a within-day and day-to-day CV of respiratory system resistance at 10 Hz (R_{10}) of 8.56% and 10.79%, respectively; in contrast, the respective CV for FEV_1 was 2.35% and 2.21%. Similarly, Neild and colleagues[22] reported the day-to-day CV for R_{10} and FEV_1 as 11.3% and 3.1%, respectively. Our data, in conjunction with previous reports, suggest that although more variable than FEV_1, respiratory system impedance remains fairly constant over 3 months.

Of perhaps greater importance is the appreciable number of COPD subjects with normal impedance parameters. We observed that respiratory system resistance and reactance, although impaired in the group as a whole, is not altered in all patients with COPD nor is it related specifically to the severity of the underlying airflow limitation. In particular, these baseline data suggest that regardless of the severity of airflow limitation, COPD subjects with normal respiratory system impedance (specifically AX and to a lesser extent resistance at 5 Hz) may represent a distinct clinical subtype, in that they appeared to have somewhat better spirometry.

These data also suggest that there may exist a subpopulation of 'apparently healthy' smoking individuals, identified by having an elevated AX, who may have early evidence of mild airflow limitation. One could speculate that this group may represent individuals with 'small airways' disease. However, the resolution of our CT images does not allow us to look specifically at airways $\leq$2 mm in internal diameter in order to relate these physiologic observations with the anatomical correlate of interest. Thus, these initial data need to be interpreted with caution.

It has long been accepted that the early pathological change in COPD patients is a respiratory bronchiolitis that begins in the small airways.[23–25] These early changes result in an inhomogeneity of the mechanical properties of the lung that can be assessed by modalities such as the frequency-dependent nature of measured compliance,[26] resistance[27,28] or the multiple-breath nitrogen washout test.[29] It had been previously suggested that abnormalities in indices from the 'effort-independent' portion of the spirometric flow-volume loop (FEF_{25-75}) may be indicative of disease in the small airways in individuals with a normal FEV_1.[30] We found a weak association between FEF_{25-75} and $R_5 - R_{20}$ in the controls and COPD subjects. Although some investigators have reported a relationship between structural changes in the small airways and FEF_{25-75},[31,32] the correlations are fairly modest ($\sim$0.4), or non-existent.[33] Actually, the variability of the measurement is large, with an average CV of 25%.[34] Thus, our inability to find a strong correlation is not too surprising.

Our findings are also in agreement with earlier reports that demonstrated minimal frequency dependence of resistance in COPD subjects that is not evident in healthy subjects.[8] We expand upon these early reports and show that the magnitude of this frequency dependency increases with worsening airflow limitation as determined by GOLD

status. However, it would not be totally correct to infer that this index of lung heterogeneity is solely related to the severity of airflow limitation as measured by spirometry. For example, Dellacà and colleagues have recently shown that this frequency dependency is more evident in those COPD subjects with demonstrable expiratory flow limitation (EFL) compared with subjects without flow limitation.[35] Moreover, only the subjects with EFL demonstrated an improvement in R_{rs} (specifically, the inspiratory component) and frequency dependency of resistance with inhaled salbutamol.[35] These authors also reported a greater decrease in R_{rs} and $R_5 - R_{19}$ in bronchodilator responders compared with non-responders. Although in our study impedance parameters were not partitioned between the inspiratory and expiratory phases of respiration, we also found that the decrease in IOS resistance following bronchodilators, as with the improvement in FEV_1, appears related to underlying severity of airflow limitation.

There are a limited number of studies that have provided impedance parameters from a normal, non-smoking population.[19,36–38] Most of these studies that derived normal values generated forced oscillations using pseudo-random noise.[19,36–37] The largest of these studies was conducted by Pasker et al, whose group generated data in 226 healthy, non-smoking subjects (126 males/106 females) at frequencies between 6 and 24 Hz.[19] Applying the regression equations provided in their paper to our non-smoking control subjects generates reactance (±SD) at 6 Hz of -0.05 ± 0.01 kPa/L/s, and resistance at 6 Hz and 20 Hz of 0.28 ± 0.03 and 0.29 ± 0.02 kPa/L/s, respectively. Conversely, Kohlhäufl and colleagues reported impedance data on 55 (30 male/25 females) healthy non-smokers[38] using a multifrequency IOS system as in the current study. Values provided for X_5, R_5, R_{20} and F_{Res} were approximately −0.10, 0.30, 0.25 kPa/L/s and 10.8 Hz, respectively. Thus, other than a somewhat lower resonant frequency, the resistance and reactance values previously reported with both pseudo-random noise and IOS techniques are not too dissimilar from those we observed. The age of our healthy non-smokers were older than those in previous studies (e.g. mean age 29–33 years in the report by Pasker and colleagues[19] and 37 years in the Kohlhäufl et al paper[38]) with a mean age of 54 years in our cohort. Coe et al reported a small increase in resonant frequency as well as an increase in resistance at 6 Hz in some (but not all) healthy, non-smokers over age 45 years compared with younger non-smokers.[37] However, Pasker reported that although statistically significant, age had a quantitatively weak effect on FOT reactance and resistance, and as such was not included in their regression equations.[19]

In summary, we have shown that impulse oscillometry can be used in large cohorts of subjects to assess respiratory system impedance. The reproducibility of such measurements in this larger multi-center study extends those previously reported in smaller, single center studies. Similarly, at lower oscillation frequencies this modality appears to be able to assess lung heterogeneity. As we hypothesized, impulse oscillometry did not simply track changes in spirometry but could be used to define different subgroups of COPD patients. The longitudinal data obtained with IOS from the ECLIPSE trial should provide additional information as to the usefulness of this modality as an independent and/or adjunctive predictive endpoint for COPD morbidity.

Conflict of interest

CC is an employee of GlaxoSmithKline; **BC** has received grants to the pulmonary division he works in to complete research studies from GlaxoSmithKline, Boehringer-Ingelheim, Forrest Medical, AstraZeneca and Aeris. BC has served on advisory boards for GlaxoSmithKline, Boehringer-Ingelheim, Almirall, AstraZeneca, Aeris and Deep Breeze, and has received speaker fees from GlaxoSmithKline, Boehringer-Ingelheim, AstraZeneca, Almirall and Esteve; **LDE** is an employee of GlaxoSmithKline and hold stocks and stock options in GlaxoSmithKline; **EW** serves on an advisory board for Nycomed. EW has received lecture fees from GlaxoSmithKline, AstraZeneca and Novartis, and has received research grants from GlaxoSmithKline and AstraZeneca; **HOC** has received an honorarium for serving on the steering committee for the ECLIPSE project for GlaxoSmithKline. In addition, HOC was the co-investigator on two multi-center studies sponsored by GlaxoSmithKline and has received travel expenses to attend meetings related to the project. HOC has three contract service agreements with GlaxoSmithKline to quantify the CT scans in subjects with COPD and a service agreement with Spiration Inc. to measure changes in lung volume in subjects with severe emphysema. HOC is the co-investigator (D Sin PI) on a Canadian Institutes of Health – Industry (Wyeth) partnership grant, and has received a fee for speaking at a conference and related travel expenses from AstraZeneca (Australia); **RT-S** is an employee and shareholder of GlaxoSmithKline, the sponsor of ECLIPSE; **PMAC** has received consulting fees from AstraZeneca, GlaxoSmithKline, Nycomed and Pfizer, speaking fees from GlaxoSmithKline and Nycomed, and grant support from Boehringer-Ingelheim and GlaxoSmithKline.

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Supplementary data

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